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Publication Title:

PHARMACEUTICAL COMPOSITION FOR TREATING OBESITY

Abstract:

A salt of N,N' sebacoyl bis-sarcosine [S(Sar)>2<] having the formula (CH>2<)>8<-[CO-N(CH>3<)-CH>2<-COOH]>2< (SBS) with L-arginine or L-lysine is used for the treatment of obesity.

A salt of N,N' sebacoyl bis-sarcosine [S(Sar)2] having the formula (CH2)8-[CO-N(CH3)-CH2-COOH]2 (SBS) with L-arginine or L-lysine is used for the treatment of obesity.

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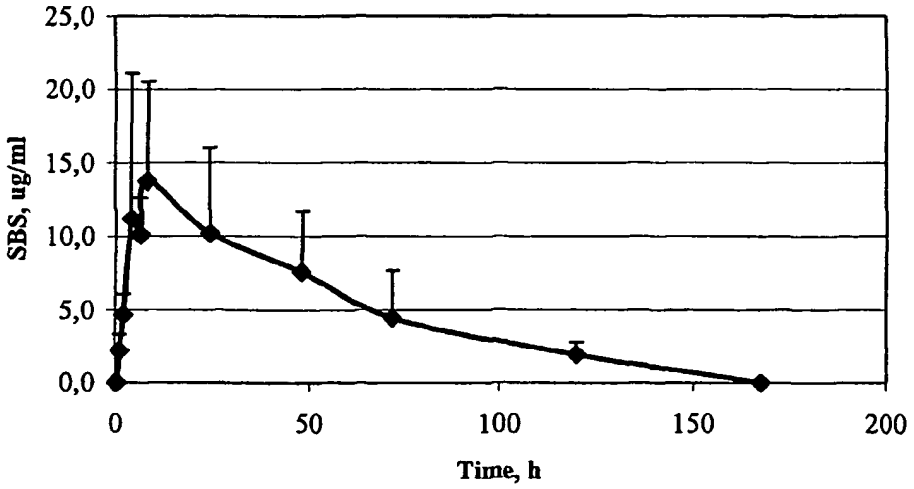
(54) Title: PHARMACEUTICAL COMPOSITION FOR TREATING OBESITY



(57) Abstract: A salt of N,N' sebacoyl bis-sarcosine [S(Sar)$_2$] having the formula $(CH_2)_8$-[CO-N(CH_3)-CH_2-COOH]$_2$ (SBS) with L-arginine or L-lysine is used for the treatment of obesity.

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PHARMACEUTICAL COMPOSITION FOR TREATING OBESITY

FIELD OF THE INVENTION

The present invention is in the field of treatment and prevention of obesity and atherosclerosis in human and non-human animals.

BACKGROUND OF THE INVENTION

Lipids are stored in the body mostly as fat under the skin and consumption of lipids and carbohydrates beyond the metabolic need leads to fattening. The associated medical and aesthetic problem, are a major concern in modern society.

Apart from surgery and dietary means, there is a desire for drugs which will reduce fat accumulation by inhibiting lipid and lipoproteins in the liver. The most potent drug, from the group of β,β′ tetrametyl substituted α,ω dicarboxylic acids (MEDICA), was found to be the hexadecane derivative (MEDICA 16). It was demonstrated that MEDICA, which is a non-naturally occurring fatty acid, could inhibit biosynthetic pathways of triglycerides and cholesterol in the liver.

U.S. patent 5,602,104 to Shinitzky *et al.* discloses a dietary supplement for the treatment of obesity. Among the dietary suplements that is mentioned is the compound N,N′ sebacoyl bis-sarcoeine-ethylester [$S(Sar)_2$] having the formula $(CH_2)_8$-[CO-N(CH_3)-CH_2-COOH]$_2$.

SUMMARY OF THE INVENTION

The present invention provides a new SBS formulation wherein the SBS is provided in the form of a salt, with the salt forming anion being L-arginine and or L-lysine. In addition to serving as a source for the nutritionally important amino acid - L-arginine or L-lysine, this salt formulation adds in a synergistic manner a clinically proved absorption of the SBS.

By a first of its aspects, the present invention thus provides a method for the treatment of obesity comprising administering to a subject an effective amount of SBS in the form of a salt, with the salt forming anion being L-arginine or L-lysine. The method of the invention is applicable to both human and non-human animals. The SBS can be administered, in accordance with the invention, parenterally, orally, topically, with oral administration being preferred. A suitable oral administration is a capsule or a pill, but other oral administration formulations, such as a drink or a syrup, are not excluded.

By another of its aspects the present invention provides a pharmaceutical composition comprising, as its active ingredient, an effective amount of SBS in a salt form, with the salt-forming anion being L-arginine or L-lysine. A particular use of the pharmaceutical composition is in the treatment of obesity. As will be appreciated, the term *"pharmaceutical composition"* should be understood in the broadest sense and includes, in its scope, a pharmaceutical composition intended as a drug that is indicated for treatment of a certain disease or condition, a cosmetic composition or another composition intended to be used in a non-medicated fashion, e.g. a composition sold over the counter (OTC) without a implied indication, as well as a composition intended for veterinary use.

By another of its aspects the present invention provides use of SBS in the form of a salt, with the salt forming anion being L-arginine or L-lysine, for the preparation of a pharmaceutical composition, particularly a pharmaceutical composition for the treatment of obesity.

The effective amount is an amount which is effective to cause the treated subject, upon repeated administration, to reduce the amount of the fat in its body and hence its weight. As will be appreciated, the effective amount depends on factors such as the administration regime, for example whether the pharmaceutical composition is administered to the individual several times, e.g. twice daily, once a day, once every two days, once every week, etc. Additionally, the effective amount may also depend on the weight of the treated individual, on its gender, on age or on a number of other physiological parameters. In addition, the effective amount may

also depend on other factors such as diseases the individual has, other drug treatments the individual receives, etc.

In another aspect, the present invention also provides a use of SBS in combination with L-Arginine or L-lysine, for the preparation of a pharmaceutical composition for the treatment of obesity. The use of SBS can be applied to both human and non-human animals and be administered both topically and orally in a preferably but not limited to capsule form.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, one preferred embodiment will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 shows serum SBS level in rabbits after a single oral dose of SBS in the form of SBS-L-arginine immediate release tablets (n = 4 animals in each case);

Fig. 2 shows the serum SBS level in rabbits after a single oral dose of SBS in the form of floating tables (n = 4 animals in each case);

Fig. 3 shows the serum level in rabbits after a single oral dose of SBS in the form of immediate-release tablets (n = 4 animals in each case);

Fig. 4 shows the serum SBS level in rabbits after a single oral dose of SBS in the form of sustained release tablets (n = 4 animals in each case);

Fig. 5 shows the serum SBS level in rabbits after a single dose of SBS in the form of enterocoating tablets (n = 4 animals in each case); and

Fig. 6 shows the serum SBS level in rabbits after a single dose of SBS in the form of SBS-Na salt solution (n = 4 animals in each case).

DETAILED DESCRIPTION OF THE INVENTION

In the Example bellow, the invention will be illustrated by a pharmaceutical composition in which L-arginine is used as the salt-forming anion. As L-arginine and L-lysine are chemically similar, the results shown below demonstrate the superiority of the L-arginine-comprising composition of the

invention over other compositions of SBS, permits to predict that compositions of the invention with L-lysine the salt-forming anion, will behave in a similar manner.

EXAMPLE COMPARATIVE PHARMACOKINETIC EVALUATION OF DIFFERENT SBS FORMULATIONS (ORAL DOSAGE FORMS) IN RABBITS

36 New Zealand male rabbits (4 animals per Formulation's group), 4-6 months old, 2.7-2.9 kg body weight, were given orally the tested tablets, (see Table 1 below) in the morning, after a night of starvation. Blood samples were collected from an ear vein into serum tubes at different time points up ranging from 15 mins. to 7 days after single-dose administration: 15 min, 30 min, 45 min, 1h, 1.5 h, 2h, 4h, 6h, 8h, 24h, 48h, 72h, 96h, 120h, 144h, 168h. Serum was separated by centrifugation. SBS concentration in rabbit's serum was tested by analytical HPLC validated method with sensitivity of 0.5 to 1 ug/ml. Pharmacokinatic analysis was calculated using the Extravascular (model 200) noncompartmental analysis (NCA) of Win NoNlin program (WinNonlin® Copyright ©1998-1999, Pharsight Corporation) version 3.1 build 168.

The maximum SBS serum concentration was achieved using SBS-L-Arginine tablets (16.8 ug/ml).

The figures illustrate the results from Tables 2A and B. Fig 1. shows serum SBS level in rabbits after a single oral dose of SBS in the form of SBS-L-Arginine immediate release tablets. It can be seen that after a quick increase in the SBS levels, it rapidly and constantly disappears.

Fig 2 shows serum SBS level in rabbits after a single oral dose of SBS in the form of floating tablets. It can be seen that it reached maximal levels at a somewhat lower rate than that seen in Fig. 1 and also a lower maximal line.

Fig 3 shows serum SBS level in rabbits after a single oral dose of SBS in the form of immediate release tablets. It can be seen that the peak of SBS is reached only after about 50h.

Fig 4 shows serum SBS level in rabbits after a single oral dose of SBS in the form of sustained release tablets. It is demonstrated that immediately after the SBS

was given, the SBS level reach its peak (lower than demonstrated in Fig 2) and begins its decline immediately after.

Figs 5 and 6 show serum SBS level in rabbits after a single oral dose of SBS administered in enterocoated tablets and in the form of sodium salt solution, respectively. It can be seen that the amount of SBS rises very slowly to its highest level (much lower than the rate seen in Fig. 1) and remains in a constant level for a long time. Furthermore, the maximal level is dramatically lower than that seen in Fig. 1.

Tables referred to above, are shown below. In these tables the following abbreviations will be used to denote the following pharmacokinetic parameters:

Tmax: Time of maximum observed concentration.

Cmax: Concentration corresponding to Tmax.

T last: Time of last measurable (non-zero) concentration.

C last: Concentration corresponding to Tlast.

$T_{1/2}$: Half-life time.

AUC: Area under the curve.

Vz, Vz/F: Volume of distribution based on the terminal phase.

CL, CL/F: Total body clearance.

MRT last: Mean residence time from the time of dosing (Dosing_time) to the last measurable concentration, for infusion models.

Table 1 – SBS tablet formulations

Formulation	SBS form	SBS per tablet, mg	Tablet weight, mg	Components
SBS-L-Arginine Immediate release tablets	Acid form	360	841.5	L-Arginine, Polyvinylpyrrolidone (USP/NF) (Kollidon K-90), Avicel, PVP XL, Magnesium Stearate
SBS Floating tablets	Acid form	450	693	Tartaric acid, Alginic acid (Kelacid™ HVCR), Sodium bicarbonate (NF grade), Polyvinylpyrrolidone (Kollidon K-30, USP/NF), Magnesium Stearate
SBS Immediate release tablets	Acid form	500	965	Microcrystalline cellulose (USP/NF) (Avicel pH102), Lactose monohydrate spray dried (USP/NF), Polyvinylpyrrolidone (USP/NF) (Kollidon K-30), Polyvinylpyrrolidone crosslinked Polyplasdone XL (USP/NF), Magnesium stearate
SBS Sustained release tablets	Acid form	450	742.5	Hydroxypropylmethylcellulose Methocel® K4M, Polyethylene oxide (MW. 900,000) Polyox™ WSRN 1105, Lactose monohydrate spray dried (USP/NF), Polyvinylpyrrolidone (USP/NF) (Kollidon K-30), Polyethylene glycol PEG 3350 (NF grade), Magnesium Stearate
SBS Enterocoated tablets	Acid form	500	965	Microcrystalline cellulose (USP/NF) (Avicel pH102), Lactose monohydrate spray dried (USP/NF), Polyvinylpyrrolidone (USP/NF) (Kollidon K-30), Polyvinylpyrrolidone crosslinked Polyplasdone XL (USP/NF), Magnesium stearate, Eudragit L-30D

Table 2. A. Model-independent pharmacokinetic parameters for SBS following single oral administration of different tablet forms in NZ Rabbits

Pharmacokinetic parameter	Units	SBS-L-Arginine Immediate release tablets		SBS Floating tablets		SBS Immediate release tablets	
		Average	Stand.dev.	Average	Stand.dev.	Average	Stand.dev.
T max	hr	**5.50**	1.91	**51.00**	19.90	**56.00**	13.86
C max	ug/mL	**16.83**	8.70	**11.48**	2.05	**10.73**	1.31
T last	hr	**108.00**	24.00	**150.00**	36.00	**141.33**	25.40
C last	ug/mL	**2.03**	0.67	**0.49**	0.27	**4.40**	3.40
T ½	hr	**36.51**	13.12	**17.10**	7.37	**81.40**	60.56
AUC all	hr*ug/mL	**777.57**	375.75	**844.31**	230.70	**992.80**	85.87
Vz / F	L/kg	**39.4**	25039.11	**14.4**	6276.53	**34.9**	11766.42
Cl / F	mL/hr/kg	**734.16**	425.17	**608.93**	205.54	**383.32**	174.44
MRT last	Hr	**37.62**	7.61	**59.25**	8.20	**72.50**	13.65

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Table 2. B. Model-independent pharmacokinetic parameters for SBS following single oral administration of different dosage forms in NZ Rabbits

Pharmacokinetic parameter	Units	SBS Sustained release tablets		SBS Enterocoated tablets		SBS-Na-salt solution	
		Average	Stand.dev.	Average	Stand.dev.	Average	Stand.dev.
T max	hr	**40.00**	13.86	**72.00**	33.94	**11.33**	11.68
C max	ug/mL	**7.77**	1.45	**11.45**	3.75	**9.10**	1.85
T last	hr	**136.00**	27.71	**168.00**	0.00	**72.00**	0.00
C last	ug/mL	**2.60**	1.35	**3.25**	0.07	**4.70**	2.75
T ½	hr	**49.94**	30.11	**48.72**	2.09	**88.63**	68.07
AUC all	hr*ug/mL	**736.28**	19.16	**1110.75**	142.48	**540.48**	179.09
Vz / F	L/kg	**32.01**	14268.84	**28.58**	1925.28	**89.44**	35612.27
Cl / F	mL/hr/kg	**480.27**	94.69	**406.40**	9.94	**983.06**	732.25
MRT last	hr	**63.17**	16.31	**76.97**	10.76	**35.37**	2.19

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CLAIMS:

1. A method for the treatment of obesity comprising administrating to a subject N,N′ sebacoyl bis-sarcoeine-ethylester [$S(Sar)_2$] having the formula $(CH_2)_8$-[CO-N(CH_3)-CH_2-COOH]$_2$ (SBS) in the form of a salt with L-Arginine or L-lysine as the salt-forming anion.

2. A method according to Claim 1, wherein the administration is oral.

3. A method according to Claim 2, wherein the SBS is administered in the form of a pill or a capsule.

4. A method according to Claim 1, wherein the SBS is administered to treat obesity.

5. A method according to Claim 1, wherein the subject is a non-human animal.

6. A method according to Claim 1, wherein the subject is a human.

7. A pharmaceutical composition comprising an effective amount of N,N′ sebacoyl bis-sarcoeine-ethylester [$S(Sar)_2$] having the formula $(CH_2)_8$-[CO-N(CH_3)-CH_2-COOH]$_2$ (SBS) in the form of a salt with the salt forming anion being L-Arginine or L-lysine.

8. A pharmaceutical composition according to Claim 7, for the treatment of obesity.

9. A pharmaceutical composition according to Claim 8, for oral administration.

10. A pharmaceutical composition according to Claim 9, in the form of a pill or a capsule.

11. A pharmaceutical composition according to Claim 7, for use in the treatment of obesity.

12. A pharmaceutical composition according to Claim 11, for the treatment of a non-human animal.

13. A pharmaceutical composition to Claim 9, for the treatment of a human.

14. Use of N,N′ sebacoyl bis-sarcoeine-ethylester [S(Sar)$_2$] having the formula $(CH_2)_8$-[CO-N(CH_3)-CH_2-COOH]$_2$ (SBS) in a salt form with L-Arginine or L-lysine as the salt-forming anion, for the preparation of a pharmaceutical composition for the treatment of obesity.

15. Use according to Claim 14, for the preparation of an oral pharmaceutical composition.

16. Use according to Claim 15, for the preparation of a pharmaceutical composition.

17. Use according to Claim 14, for the preparation of a pharmaceutical composition for the treatment of obesity.

18. Use according to Claim 14, for the preparation of a pharmaceutical composition for the treatment of a non-human animal.

19. Use according to Claim 14, for the preparation of a pharmaceutical composition for human use.

Figure 1.

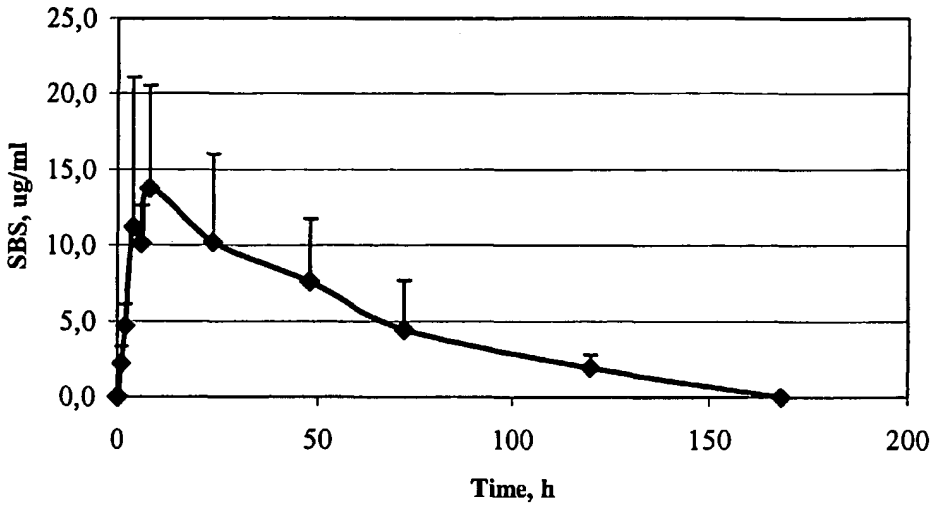


Figure 2.

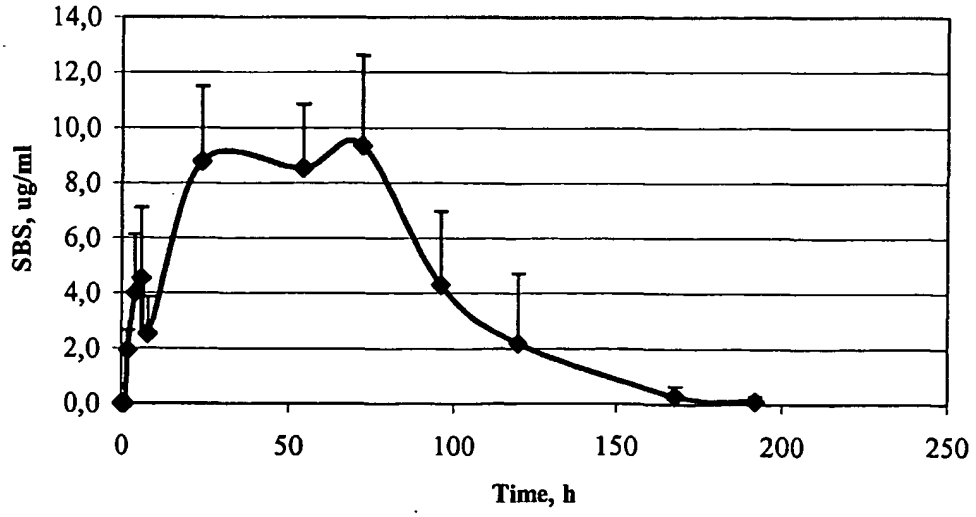


Figure 3.

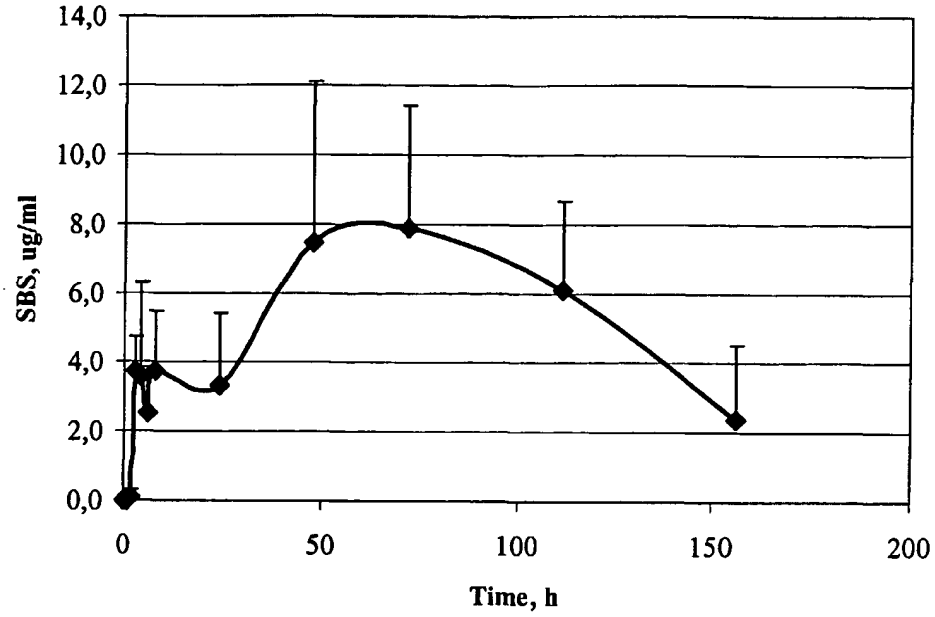


Figure 4.

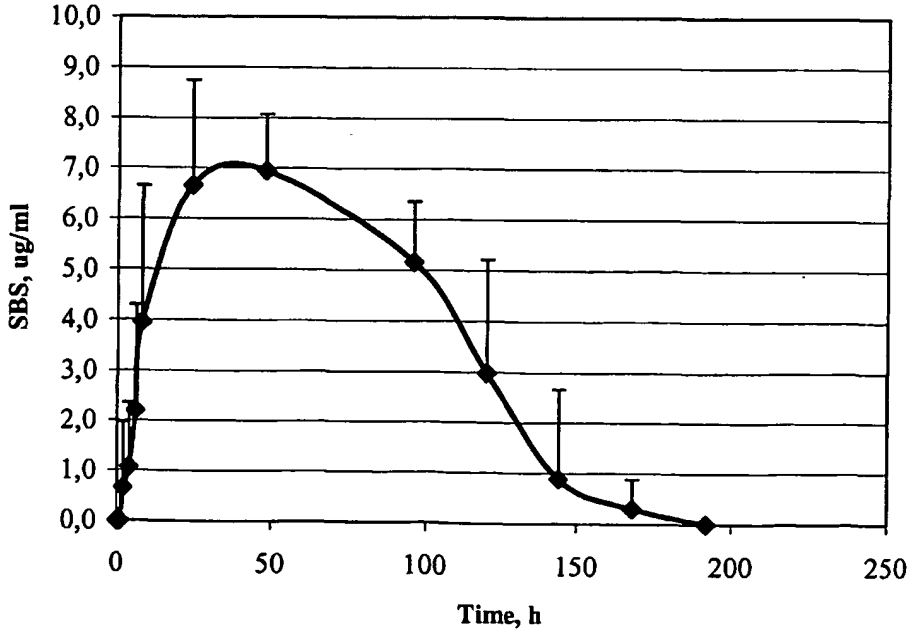


Figure 5.

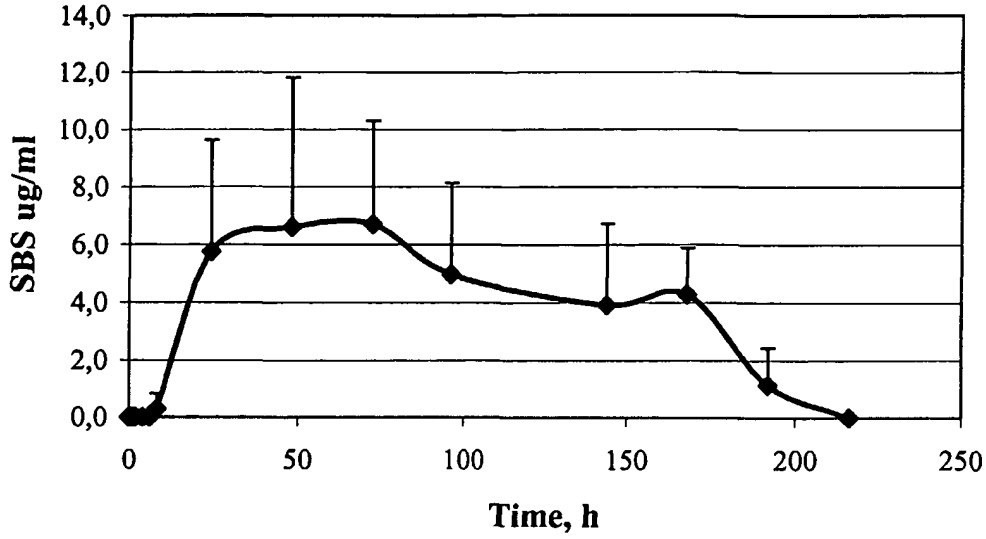
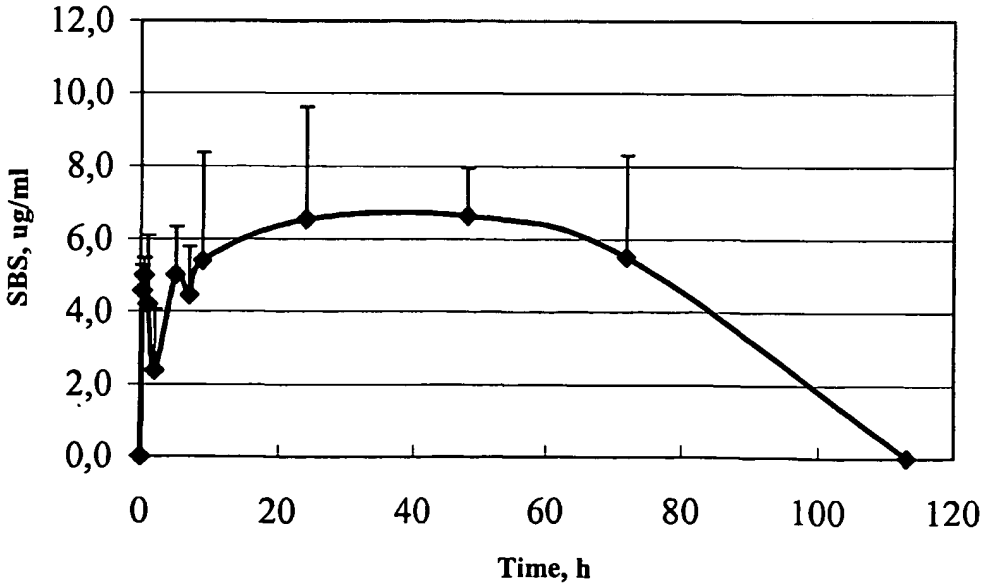


Figure 6.



INTERNATIONAL SEARCH REPORT

[redacted] al Application No
[redacted] /AU 01/02227

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61K31/198 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 21913 A (SENYORINA LTD ;COHN MICHAEL (IL); SHINITZKY MEIR (IL)) 11 November 1993 (1993-11-11) cited in the application abstract page 3, line 10 - line 14 page 3, line 22 -page 4, line 13 page 5, line 5 - line 8 figure 2 page 7, line 21 - line 28 page 8, line 16 - line 17 claims --- -/--	1-19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 July 2002	29/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cielen, E

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	PRUEKSARITANONT T ET AL: "ABSORPTION OF IOTHALAMATE AFTER ORAL ADMINISTRATION AND ABSORPTION ENHANCEMENT BY AMINO-ACIDS IN DOGS AND RATS" BIOPHARMACEUTICS & DRUG DISPOSITION, vol. 7, no. 5, 1986, pages 463-478, XP008005722 ISSN: 0142-2782 abstract page 464, paragraph 2 page 466, paragraph 3 - paragraph 4 page 468, paragraph 4 page 472, paragraph 2 - paragraph 3 figure 4 page 473, paragraph 3 page 474, paragraph 1 page 477, paragraph 3 ---	1-19
A	MOOTE CAROL A: "Ibuprofen arginine in the management of pain: A review." CLINICAL DRUG INVESTIGATION, vol. 11, no. SUPPL. 1, 1996, pages 1-7, XP008005721 ISSN: 1173-2563 abstract page 2, column 2, paragraph 2 - paragraph 3 page 3, column 2, paragraph 2 -page 4, column 1, paragraph 1 page 6, column 1, paragraphs 3,5 ---	1-19
A	EP 0 066 934 A (PHARLYSE) 15 December 1982 (1982-12-15) page 1, line 21 -page 2, line 24 page 8, line 13 - line 19 claims 1-3 ---	1-19
A	EP 0 140 492 A (WARNER LAMBERT CO) 8 May 1985 (1985-05-08) abstract page 1, line 8 - line 13 page 2, line 4 - line 8 page 3, line 3 - line 23 -----	1-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 01/02227

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/02227

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